MEMO

To: YNHHS Medical Staff

From: YNHHS ICU Committee

Subject: SBAR: Alternative Drug Shortage Guide (Sedatives, Analgesics, Paralytics)

Date: May 9, 2021

Situation: There is a need to provide guidance on currently available and alternative therapies for sedation, analgesia and paralysis.

Background: As a result of the increase in volume of COVID-19 critically ill patients, there is a nationwide shortage in commonly used sedatives, analgesics and paralytics. Several alternative medications have been acquired to meet the increased demand for these therapies. Additionally, there is an ongoing expansion of critical care units and familiarizing staff with these newly added agents is warranted.

Assessment: There is a need for an alternative therapy guide to familiarize clinicians with available therapies for sedation, analgesia, and paralysis.

Recommendation: The alternative drug therapy guide below will provide guidance to clinicians on existing and alternative therapies.

Sedatives, Analgesics, Neuromuscular Blocking Agents – Alternative Drug Shortage Guide

Drug supply is inconsistent and changes frequently, alternative therapies will be guided based on drug availability

ANALGESICS

Analgesia Management (current inventory may determine selection)
Preferred: Morphine, fentanyl (preferred in AKI, CKD, and RRT)
Alternative: Hydromorphone (continuous infusion) -pharmacist order entry (patients with high opioid requirements; receiving 10 mg IV morphine per hour for at least 2 hours)
Remifentanil - pharmacist order entry
Ketamine - pharmacist order entry (patient with adverse reaction to hydromorphone and when remifentanil not available)
Adjunct therapy: Enteral acetaminophen, tramadol, gabapentin, oxycodone, methadone

SEDATIVES

Sedation Management (optimize pain management, current inventory may determine selection)
Preferred: Dexmedetomidine (not for deep level of sedation)
Propofol
Alternative:Lorazepam (use with caution in hepatic and renal dysfunction)
Midazolam (use with caution in hepatic and renal dysfunction)
Ketamine - pharmacist order entry, third-line agent, restricted to the following:
- Escalating doses or contraindication to propofol (≥65 mcg/kg/min or TG >600 mg/dL)
- Escalating doses to midazolam/lorazepam (≥10mg/hr) or contraindication to midazolam (cirrhosis, AST/ALT >5xULN) and lorazepam (Osmol gap >10 mOsm/kg)

Phenobarbital monotherapy for management of alcohol withdrawal syndrome
Adjunct therapy: to lower sedation requirements; phenobarbital, enteral clonidine, atypical antipsychotic (quetiapine, olanzapine)

PARALYTICS

Neuromuscular blocking agents continuous infusion (adequate sedation and analgesia required prior to and during paralysis, current inventory may determine selection)
Preferred: Rocuronium
Cisatracurium - pharmacist order entry (preferred in AKI, CKD, RRT, and/or hepatic dysfunction)
Alternative: Atracurium - pharmacist order entry (preferred in AKI, CKD, RRT, and/or hepatic dysfunction and cisatracurium not available)
Critical shortage: Vecuronium

Neuromuscular blocking agents for rapid sequence intubation current inventory may determine selection
Preferred: Succinylcholine
Alternative: Rocuronium

AKI: acute kidney injury; CKD: chronic kidney disease (CrCl <30 mL/min); RRT: renal replacement therapy; TG: serum triglyceride (mg/dL); ULN: upper lower limit of normal

Drug	Mechanism of action	Dosing recommendation	Side effects and considerations
ANALGESICS (continuous infusion therapy for mechanically ventilated patients)			
Morphine 100 mg/100 mL (1 mg/mL)	Opioid (mu)-receptor agonist	MD: 1 -10 mg/hr Titrate by: 1 mg/hr Frequency: No more than every 15 minutes Maximum dose: 10 mg/hr IV Bolus: 2-4 mg IV q 4 hr PRN or scheduled	Hypotension and bradycardia can occur due to histamine release. Avoid in renal dysfunction due to accumulation of active metabolite. Use with caution in hepatic dysfunction. Can cause respiratory depression, CNS depression, constipation, and ileus.
Hydromorphone 40 mg/100 mL (0.4 mg/mL)		MD: 0.2 – 5 mg/hr Titrate by: 0.2 mg/hr Frequency: No more than every 30 minutes Maximum Dose: 5 mg/hr IV Bolus: 0.5 – 1 mg IV q 2 hr PRN or scheduled	Hydromorphone is 5 - 7 times MORE POTENT than morphine. Use lower doses in opioid-naïve patients. Use with caution in hepatic dysfunction. Can cause respiratory depression, CNS depression, constipation, and ileus.
Remifentanil 5000 mcg/100 mL (50 mcg/mL)		MD: 0.5 – 12.5 mcg/kg/hr Titrate by : 1.5 mcg/kg/hr Frequency: No more than every 5 minutes Maximum dose: 12.5 mcg/kg/hr Use actual body weight. Use ideal body weight (IBW) if patient's actual weight is 130% > IBW IV Bolus: 25 – 100 mcg every 30 min PRN	Monitor for opiate withdrawal symptoms for 24 hours after discontinuing Remifentanil. Consider x1 dose of morphine/hydromorphone injection prior to remifentanil infusion discontinuation. Can cause chest wall rigidity. Drug clearance occurs by blood and tissue esterases. Can cause respiratory depression, CNS depression, constipation, and ileus.
ANALGESIA ADJUNCT THERAPY (consider adjunct therapy to lower continuous infusion analgesia requirements)			
Oxycodone	Opioid (mu)-receptor agonist	PO: 2.5 – 10 mg PO q 4 hr PRN or scheduled	
Tramadol	Opioid (mu)-receptor agonist, inhibit norepinephrine and serotonin reuptake, and NMDA receptor antagonist	PO: 25 – 100 mg PO q6 hr Maximum dose: 400 mg/day	Avoid in patients with seizure disorder. Associated with serotonin syndrome Hepatically metabolized to active metabolite O-desmethyltramadol that is renally eliminated. Requires dose adjustment in renal failure
Gabapentin	Inhibits alpha 2-delta subunit of voltage-gated calcium channels → reduce neuronal hyper-excitability	PO: 300 mg – 1200 mg three times daily	Preferred therapeutic option for neuropathic pain. Adjust dose based on renal function.
Methadone	Mu-receptor agonist, NMDA-receptor antagonist	PO: 5 – 10 mg PO q8 – 12 hr scheduled	Very long half-life (up to 60 hours) Dose-dependent QTc prolongation

SEDATIVES (Continuous infusion for mechanically ventilated patients, optimize pain management)			
Propofol 1000 mg in 100 mL (10 mg/mL) 500 mg in 50 mL (10 mg/mL)		LD: Not recommended outside RSI MD: 5-80 mcg/kg/min Start: 5 mcg/kg/min Titrate by: 5 mcg/kg/min Frequency: No more than every 5 minutes Maximum Dose: 80 mcg/kg/min	Bolus and rapid dose titration can cause cardiac and respiratory depression. Propofol-related infusion syndrome (PRIS) at doses >65 mcg/kg/min for >48 hours. Tubing should be changed every 12 hours. Avoid in patient allergic to egg or soy products.
Midazolam 50 mg/50 ml NS (1 mg/mL) 100 mg/100 mL NS (1 mg/mL)	GABA modulator	LD: 0.5-1 mg MD: 0.5-20 mg/hr Start: 0.5 mg/hr Titrate by: 0.25 mg/hr Frequency: No more than every 5 minutes Maximum Dose: 20 mg/hr	Respiratory depression Use with caution in renal and hepatic impairment. Monitor for CYP-enzyme drug-drug interactions.
Lorazepam 50 mg/50 ml D5W (1 mg/mL) 100 mg/100 mL D5W (1 mg/mL)		LD: 0.5-1 mg MD: 1-20 mg/hr Start: 1 mg/hr Titrate by: 0.5 mg/hr Frequency: No more than every 15 minutes Maximum Dose: 20 mg/hr	Respiratory depression At high doses, propylene glycol excipient can cause hypotension, metabolic acidosis, increase in osmolality (>320 mOsm/Kg), acute tubular necrosis. Monitor arterial blood gas pH, osmolar gap, serum creatinine, and urine output. Use with caution in hepatic and renal (mild and moderate) impairment.
Dexmedetomidine 200 mcg/50 mL D5W (4 mcg/mL) 400 mcg/100 mL D5W (4 mcg/mL) 1000 mcg/250 mL NS (4 mcg/mL)-pharmacist order entry only	α_2-Adrenergic receptor agonist	MD: 0.2-1.4 mcg/Kg/hr Start: 0.2 mcg/kg/hr Titrate by: 0.1 mcg/kg/hr Frequency: No more than every 30 minutes Maximum Dose: 1.4 mcg/kg/hr	Dexmedetomidine doesn't provide deep sedation (RASS <-3) LD is not recommended, as IV push is associated with hypotension and bradycardia. Does not cause respiratory depression Can cause hypotension, bradycardia Caution with use in hepatic dysfunction Withdrawals symptoms can occur. Consider oral clonidine to taper off dexmedetomidine.
Ketamine 5000 mg in NS 500 mL (10 mg/mL) 2500 mg in NS 250 mL (10 mg/mL)	NMDA receptor antagonist	LD: 1 mg/Kg MD: 0.3 – 2 mg/kg/hr Start: 0.3 mg/kg/hr Titrate by: 0.1 mg/kg/hr Frequency: No more than every 15 minutes Maximum Dose: 2 mg/kg/hr	Contraindicated in acute decompensated heart failure. Use with caution in cerebral vascular accident and elevated intra-cranial pressures, and pulmonary hypertension. Associated with dissociative "emergence reaction" Can cause hypersalivation, lacrimation, and tachycardia Monitor for CYP-enzyme drug-drug interactions

ADJUNCT SEDATIVES (consider adjunct therapy to lower continuous infusion sedation requirements)			
PHENobarbital 65 mg/mL and 130 mg/mL vials	Long-acting barbiturate	Dose IV/IM (adjunct for sedation): 30 to 120 mg/day IV in 2 or 3 divided doses; do not exceed a rate of 60 mg/min Maximum 400 mg/day	Respiratory depression May cause hypotension. IV formulation contains propylene glycol; may cause metabolic acidosis. Monitor for CYP-enzyme drug-drug interactions
Clonidine (PO) 0.05 mg, 0.1 mg, 0.3 mg, 0.6 mg	α_2-Adrenergic receptor agonist	Oral: 0.1-0.3 mg q 6-8 hr Titrate to achieve sedation, 0.2 to 0.5 mg every 6 hours Consider as an adjunct to other sedatives	Can cause bradycardia, hypotension, and xerostomia. Can prolong effect in renal impairment. Consider to prevent dexmedetomidine withdrawal symptoms.
Olanzapine (PO/IV/IM) 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg 10 mg/vial	Atypical antipsychotic Affects central dopamine, muscarinic, serotonin receptors, and peripheral α-1 receptors	Use as adjunct therapy PO: 5 – 10 mg every 2 hours IV/IM: 1.25-10 mg repeat every 2-4 hours Maximum daily dose of 30 mg	May alter cardiac conduction and prolong the QT interval Avoid concomitant use of IV benzodiazepines as they may enhance the adverse effect of benzodiazepines (cardiorespiratory depression)
Quetiapine (PO) 12.5 mg, 25 mg, 50 mg, 100 mg, 200 mg, 300mg, 400 mg	Atypical antipsychotic Affects Serotonin, dopamine, histamine , and adrenergic receptors	PO: 50 mg BID, increase by 100 mg /day to a total dose to 400 mg/day	May alter cardiac conduction and prolong the QT interval
PARALYTICS **(adequate sedation and analgesia required prior to paralysis)**			
Rocuronium 10 mg/mL (5 ml vials) 100 mg/100 mL (1 mg/mL) 500 mg/100 mL (5 mg/mL)	Inhibit acetylcholine at motor endplate	Initial bolus: 0.6 – 1 mg/kg MD: 5 – 12 mcg/kg/min Titrate by: 1 mcg/kg/min Frequency: No more than every 20 minutes Maximum dose: 12 mcg/kg/min RSI: 1 to 1.2 mg/kg followed by 20 ml of NS flush	Appropriate alternative to succinylcholine for RSI Avoid in hepatic and renal dysfunction Can cause tachycardia
Vecuronium 40 mg/100 mL (0.4 mg/mL)		Initial bolus with rocuronium MD: 0.8 – 1.2 mcg/kg/min Titrate by: 0.1 mcg/kg/min Frequency: No more than every 30 minutes Maximum dose: 1.2 mcg/kg/min	Active hepatic and renal metabolites, avoid in hepatic and renal dysfunction

Cisatracurium 40 mg/100 mL (0.4 mg/mL) 200 mg/100 mL (2 mg/mL), pharmacist order entry only		Initial bolus with rocuronium MD: 0.5 -10 mcg/kg/min Titrate by: 0.5 mcg/kg/min Frequency: No more than every 15 minutes Maximum dose: 10 mcg/kg/min	Can cause bronchospasm, bradycardia
Atracurium 500 mg/100 mL (5 mg/mL)		Initial bolus with rocuronium MD: 5 - 20 mcg/kg/min Titrate by: 1 mcg/kg/min Frequency: No more than every 15 minutes Maximum dose: 20 mcg/kg/min	Fast administration can cause hypotension, flushing, and bronchospasm Tachyphylaxis can occur at high dose.
Succinylcholine 20 mg/mL (10 mL vials)		RSI: 1-1.5 mg/kg	Avoid in hyperkalemia May cause a transient increase in intracranial pressure.

CYP: cytochrome; GABA: gamma aminobutyric acid; IV: intravenous; IM: intramuscular; LD: initial loading dose; MD: maintenance dose; NMDA: N-methyl-D-aspartate receptor; PO: oral; RSI: rapid sequence intubation